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The Significance of the Bone Marrow Biopsy Pattern in Chronic Lymphocytic Leukemia: A Prognostic Dilemma

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Although bone marrow biopsy pattern (BMBP) has long been suggested to be an independent prognostic factor in chronic lymphocytic leukemia (CLL), conflicting reports continue to appear in the literature. To investigate this issue we retrospectively reviewed 70 CLL patients who had undergone bone marrow biopsy at the time of diagnosis in a multivariate Cox regression analysis together with other prognostic factors. There were 51 (72.8%) males and 19 (27.2%) females with a median age of 60 years (range, 38–77). The median follow-up time was 24 months (range, 1–76), and median survival was 44 months. Thirtyfour patients (48.6%) had diffuse and 36 patients (51.4%) had nondiffuse BMBP (14 nodular, 11 interstitial, and 11 mixed). The median survival for diffuse and nondiffuse BMBP groups were 17 and 53 months, respectively ($P = 0.05$). Sixteen patients (22.9%) had stage A, 28 (40.0%) stage B, and 26 (37.1%) stage C disease according to the Binet system, and four patients (5.7%) had low-risk, 39 (55.7%) intermediate-risk, and 27 (38.6%) high-risk disease according to the modified Rai staging system. The difference between the median survivals of patients in different stages was statistically significant ($P < 0.0001$). The BMBP and staging systems that are thought to be significant predictors of prognosis were used to build a multivariate Cox proportional hazard model. BMBP was not found to add additional information to the prognostic value of the staging systems. Our results underline two points: first, the significance of BMBP must be investigated in multivariate analysis including the stage, and second, BMBP is not a dynamic prognostic parameter, it is an index of tumor burden and does not add any prognostic information beyond that provided by clinical stage. Am. J. Hematol. 62:208–211, 1999.

Key words: bone marrow; biopsy pattern; chronic lymphocytic leukemia

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by a variable clinical course and survival prediction is important for the treatment decision and follow up [1]. Staging is the most frequently used prognostic parameter. However, because the clinical course may be variable even within a particular stage, other prognostic parameters are required [2]. Bone marrow biopsy pattern (BMBP) has been reported to be a distinct prognostic factor, but conflicting results about its significance in CLL in the literature continue to appear [3–9]. This procedure is invasive and expensive, thus the prognostic significance and applicability in the practice should be well established.

We investigated the prognostic value of BMBP in patients with CLL diagnosed and followed up in our center. The results were evaluated by univariate and multivariate analysis including the disease stage, and the prognostic significance of BMBP was compared to the current staging systems.

PATIENTS AND METHODS

Patients

One hundred fiftysix patients were diagnosed between January 1980 and May 1995 at the Hacettepe University Hospitals. Seventy patients who underwent bone marrow biopsy at presentation were included into the study. There were 51 (72.8%) males and 19 (27.2%) females

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TABLE I. Patient Characteristics for BMBP and Staging Systems

	N (%)	1-Year survival	3-Years survival	Median survival (mo)	*P*
BMBP					0.05
Diffuse	34 (49)	74.9 ± 9.1	49.8 ± 11.1	17	
Nondiffuse	36 (51)	96.4 ± 3.5	57.9 ± 11.8	53	
Binet					*
A	16 (23)	100 ± 0.0	75.0 ± 15.8	81	
B	28 (40)	95.5 ± 4.4	69.1 ± 12.0	44	
C	26 (37)	39.0 ± 13.3	9.8 ± 9.1	12	
Modified Rai					**
Low-risk	4 (6)	NA[a]	NA	NA	
Intermediate-risk	39 (56)	96.7 ± 3.3	73.4 ± 9.7	63	
High-risk	27 (38)	43.2 ± 13.0	8.7 ± 8.2	12	

*All groups $P < 0.0001$; A vs B, $P = 0.18$; A vs C, $P < 0.0001$; B vs C, $P = 0.004$.
**Intermediate- vs high-risk, $P < 0.0001$.
[a]NA, not available.

with a median age of 60 years (range, 38–77). The median follow-up time was 24 months (range, 1–76), and median survival was 44 months.

Diagnostic Criteria

The diagnosis of CLL was made on the basis of the following criteria: (1) lymphocytosis in peripheral blood films $>4.0 \times 10^9$/l, lasting longer than 4 weeks; (2) lymphocytic infiltration in bone marrow aspirate >30%; and (3) the determination of surface immunoglobulins by flow cytometry to support the former criteria.

Clinical Staging

The patients were staged at the time of diagnosis according to both Binet and modified Rai staging systems [10,11].

Evaluation of Bone Marrow Biopsy

Initial bone marrow specimens of 70 CLL patients were independently reevaluated by three experienced pathologists who had no knowledge of the clinical data, except for the diagnosis. All specimens were classified into four groups according to the method suggested by Rywlin [12], but three patterns (nodular, interstitial, and mixed) were collected for statistical purposes as the nondiffuse pattern and compared to the diffuse pattern.

Nodular pattern. Nodular lymphocytic infiltrates replacing the normal hematopoietic cells in some areas, but normal architecture of the bone marrow is preserved.

Interstitial pattern. Bone marrow architecture is also preserved and lymphocytic infiltrate is dispersed among the hematopoietic cells and fat spaces.

Mixed pattern. The combination of nodular and interstitial patterns.

Diffuse pattern. Diffuse lymphocytic infiltration effacing the normal marrow architecture.

Statistical Method

Median survivals were used in the statistical analysis. Difference in survival between groups was evaluated by method of Kaplan and Meier [13]. Bimodal comparison was made by Gehan test [14]. Results were also analyzed by multivariate Cox regression analysis including the patients' staging [15].

RESULTS

BMBP

The examination of the bone marrow biopsy specimen revealed that thirtyfour patients (48.6%) had diffuse and 36 patients (51.4%) had nondiffuse BMBP (14 nodular, 11 interstitial, and 11 mixed). The median survival of the diffuse and nondiffuse BMBP groups were 17 and 53 months, respectively ($P = 0.05$).

Clinical Staging Distribution

According to the Binet system, 16 patients (22.9%) had stage A, 28 (40.0%) stage B, and 26 (37.1%) stage C disease. Four patients (5.7%) had low-risk, 39 (55.7%) intermediate-risk, and 27 (38.6%) high-risk disease according to the modified Rai staging system. The difference between the median survivals of all groups was statistically significant ($P < 0.0001$). The patients' distributions according to BMBP, Binet, and modified Rai clinical staging systems and 1- and 3-year survival and median survival of the groups are presented in Table I and Figs. 1–3.

The parameters that are thought to be significant predictors of prognosis were used to build a multivariate Cox proportional hazard model excluding LDH and absolute lymphocyte count that had no or only borderline significance in the univariate analysis. BMBP was not found to give additional information to the prognostic value of the staging systems. The risk ratios of the Binet

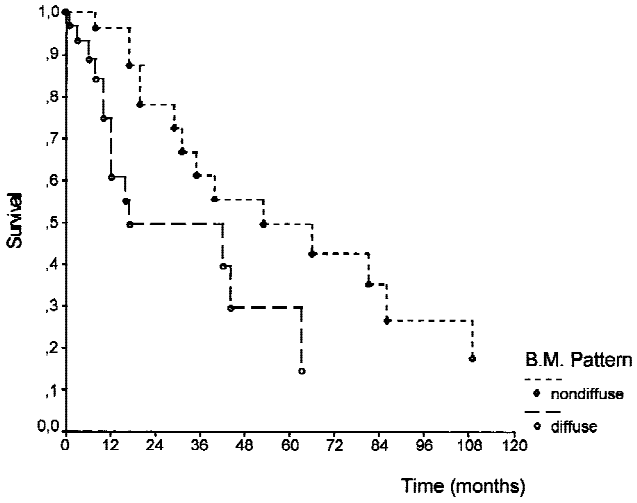

Fig. 1. Median survival of groups according to the BMBP.

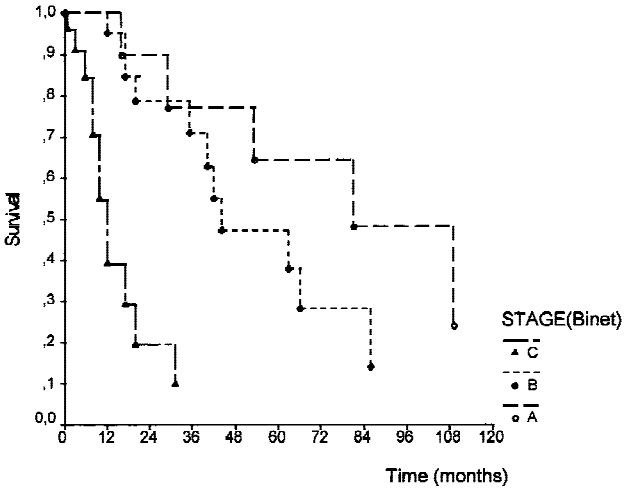

Fig. 2. Median survival of groups according to the Binet staging.

staging system and BMBP are presented in Table II. Because there were only 4 patients in modified Rai low-risk stage and all 4 patients were alive, multivariate analysis was performed only according to the Binet staging.

DISCUSSION

Despite the fact that clinical stage is the simplest and the strongest determinant in predicting the survival in patients with CLL, the heterogeneity of clinical course even within the same stage has led to a search and definition of various laboratory or clinical prognostic factors including cytogenetic changes, lymphocyte doubling time, BMBP, serum lactate dehydrogenase level, initial absolute lymphocyte count, and others, of which only a few contribute any prognostic information independent

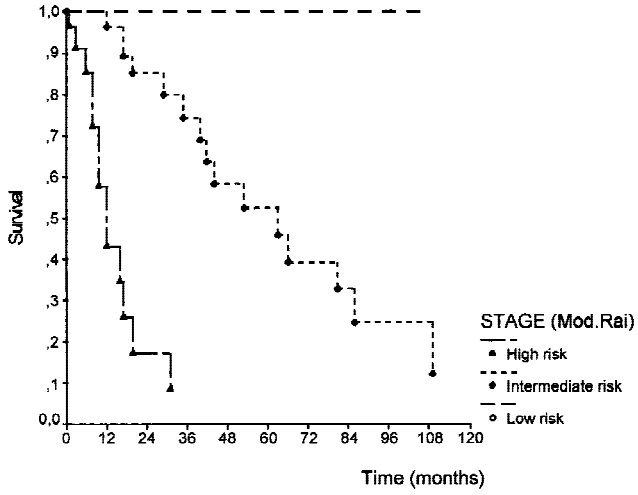

Fig. 3. Median survival of groups according to the modified Rai staging.

TABLE II. Results of the Multivariate Analysis

			95% CI[b] of risk ratio	
	P	Risk ratio	Lower	Upper
Stage	0.0004			
A vs C	0.0004	10.3	2.8	38.1
B vs C	0.0012	4.8	1.9	12.3
BMBP	0.48	NS[a]		

[a]NS, not significant.
[b]CI, confidence interval.

of stage [2]. BMBP has been the center of interest and conflict as a prognostic indicator for more than two decades. No study denies the correlation between the stage and the pattern of bone marrow involvement, all reporting a clustering of nondiffuse bone marrow involvement in the early and diffuse pattern in the late stages [3–9,16–20]. This was observed in the present study also, where 31 out of 43 patients in stages 0–1–2 according to modified Rai had nondiffuse BMBP and only 5 out of 22 patients in stages 3–4 had a nondiffuse pattern. This correlation has played a misleading role about the prognostic importance of BMBP.

Rozman et al. [5] in a retrospective analysis of 329 patients with CLL reported that patients with diffuse pattern survived a shorter time compared to those with a nondiffuse pattern and that BMBP appeared to be a stronger predictor of survival than hepatosplenomegaly, lymphadenopathy, anemia, and thrombocytopenia. Although the comparison between these parameters and BMBP favored the latter as a stronger predictive factor, even in this study BMBP failed to add to the predictive value of the clinical stage since the only significant difference was observed in the stage B patients. Pangalis et al. also reported on the positive predictive power of BMBP in several articles pointing to the early treatment

indication of CLL patients with diffuse BMBP [3,20,21]. In the first of these studies [21] 48 patients were evaluated: 27% with diffuse pattern required therapy at presentation, but 91% of these patients had stage C disease. In the second article [3] there were 120 cases where discrimination of survival difference within stages could not be made.

However, some reports have suggested that BMBP did not appear to have a predictive value beyond that provided by the clinical stage. Han et al. [22] in a prospective analysis of 75 patients reported that BMBP lost its significance when combined with the stage in a multivariate analysis. Desablens et al. [7] also found the clinical stage to be a better discriminator than BMBP in a study of 98 patients with CLL. Mauro et al. [9] reported similar findings in 335 patients with CLL about the lack of additional predictive value of BMBP as a prognostic factor within individual stages. Geisler et al. [8] recently reported that the prognostic significance of BMBP was not over that of stage in 404 B-CLL patients when overall survival was taken as the end point, although progression-free survival was significantly shorter in early-stage patients with a diffuse BMBP.

In the present study, BMBP was detected as a significant prognostic parameter in univariate analysis, but the significance disappeared when multivariate analysis was applied including the clinical stage. On the basis of this information, studies investigating the prognostic significance of BMBP must employ multivariate regression analysis taking the clinical stage into consideration.

Our results underline two points: first, the significance of BMBP must be investigated in multivariate analysis including the stage; second, BMBP is an index of tumor burden rather than being a dynamic independent prognostic parameter and does not provide any significant information beyond that provided by clinical stage.

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